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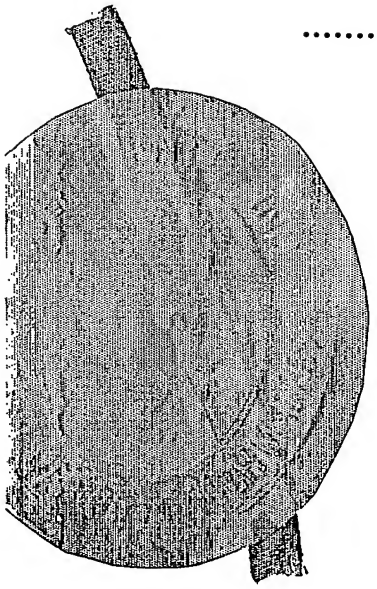
# THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of the complete specification filed in respect of Patent application No.259/MAS/2002 dated 8th April 2002 by Dr. Reddy's Laboratories Limited, an Indian Company having its registered office at 7-1-27, Ameerpet, Hyderabad – 500 016, Andra Pradesh, India .....



.....In witness thereof

I have hereunto set my hand

Dated this the 17th day of May2002
27th day of Vaisakha, 1924 (Saka)

(K.M. VISWANATHAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
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# FORM-2

THE PATENTS ACT, 1970

# COMPLETE SPECIFICATION

(SECTION 10)

**Novel anhydrous form of 1 – Cyclopropyl – 6 – fluoro – 8– Methoxy- 7 – (3 – methyl –1–piperazinyl) – 4 – oxo – 1, 4 -dihydroquinoline –3 – carboxylic acid (Gatifloxacin)**

**Dr. Reddy's Laboratories Limited,**
**An Indian Company having its registered office at**
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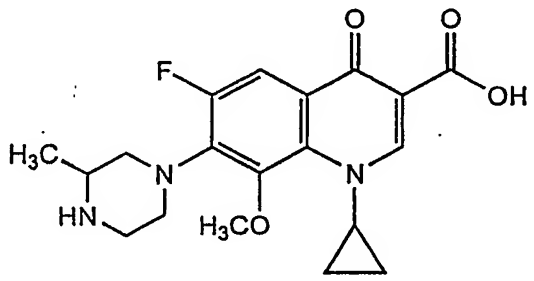
**Hyderabad-500 016, A.P., India.**

The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

## FIELD OF THE INVENTION

The present invention relates to the novel anhydrous crystalline form of 1 – Cyclopropyl – 6 – fluoro – 8– Methoxy- 7 – (3 – methyl –1 –piperazinyl) – 4 – oxo – 1, 4 -dihydroquinoline –3 – carboxylic acid. It is generically known as Gatifloxacin and marketed under brand name "Tequin".

The present invention also relates to method of making the anhydrous form of Gatifloxain, which can be depicted as Formula (1).




Formula (1)

Gatifloxacin and its pharmaceutically acceptable salts are useful as antibiotics.

## BACK GROUND OF THE INVENTION

Quinolone carboxylic acid derivatives constitute a class of extremely potent and orally active broad-spectrum antibacterial agents. Several structural activity relationship (SAR) and quantitative structure activity relationship (QSAR) studies have led to the discovery of important class of quinolines called fluoroquinolones.

Gatifloxacin of Formula (1) belonging to the class of the said fluoroquinolones is significantly noted because of not only its potent antibacterial activity but also higher selectivity against bacteria from mammalian cells, which brings on an excellent selective toxicity.

Gatifloxacin is administered orally and intravenously. The usual dose of Gatifloxacin is 400mg once daily.

Several references disclosed the structure of Gatifloxacin and **USP 4,980,470,** incorporated here in by reference, describe the synthesis of Gatifloxacin hemihydrate. Gatifloxacin hemihydrate is prepared by condensing 1-cyclopropyl-6, 7- difluoro-1, 4-dihydro-4-oxo-8-methoxy quinoline-3-carboxylic acid with 2-methyl piperezine in DMSO, accompanied by chromatographic purification. The invention also includes the process for the preparation of various piperazine derivatives and their different salts, which are useful as antibacterial agents.

**US 5,880,283** disclosed preparation of the Gatifloxacin sesquihydrate, which involves heating the mixture of 1 – Cyclopropyl – 6 – fluoro – 8– methoxy- 7 – (3 – methyl –1– piperazinyl) – 4 – oxo – 1, 4 -dihydroquinoline –3 – carboxylic acid with water, preferably 3-5 times over the weight of reactant at 80-85$^{o}$C and subsequent filtration and drying resulting in the sesqui hydrate of Gatifloxacin.

Japanese unexamined patent publication 63-198664, discloses Gatifloxacin hydrochloride salt is disclosed. The patent stated that hemihydrate and hydrochloride of Gatifloxacin is unstable due to their hygroscopic nature of the drug substance, and the problems are encountered due to its poor disintegration and dissolution rate while formulating the tablets.

The present invention is directed to anhydrous form of Gatifloxacin, which is non-hygroscopic, crystalline and non-solvated, generally, the hygroscopic nature will results due to the presence of impurities, but the present inventive substance is non-hygroscopic, which infers the high purity of the compound. The present inventive substance has produced in non-solvated form, i.e., the content of residual solvents are well within the limits as per ICH guidelines; hence it is very well suited for pharmaceutical formulations.

The present invention of anhydrous form of Gatifloxacin is having moisture content from 0.05% to 2.0% by KF and as per thermo gravimetric analysis, which is less than the hemi hydrate.

The crystalline nature of the present anhydrous inventive substance is characterized by its X-ray diffractogram, Differential Scanning colorimetry thermogram and IR spectrum.

Hence, the objective of the present invention is to provide a novel anhydrous crystalline form of Gatifloxacin.

Another objective of the present invention is to provide a process for the preparation of anhydrous crystalline form of Gatifloxacin, which is cost effective, commercially viable and well suited for industrial scale up.

## SUMMARY OF THE INVENTION

The present invention is directed to novel anhydrous crystalline form of Gatifloxacin. The present invention also provides the process for the preparation of anhydrous crystalline form of Gatifloxacin, which comprises the azeotropic removal of water from hydrated form of Gatifloxacin at reflux temperature using an aromatic/aliphatic hydrocarbon solvent or a ketone solvent. The process is commercially viable and well suited for industrial scale up.

## BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig.1 is a diagram showing the results of thermo gravimetric analysis of the inventive substance.

Fig. 2 is a diagram showing the results of X-ray diffraction of the inventive substance.

Fig. 3 is a diagram showing the results of DSC of the inventive substance.

Fig. 4 is a diagram showing the results of IR spectrum of the inventive substance.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides the novel anhydrous crystalline form of Gatifloxacin of Formula (1) and a process for the preparation thereof.

The crystalline nature of novel anhydrous form of Gatifloxacin of present invention may be characterized by its X-ray diffractogram, Differential Scanning colorimetry thermogram and IR spectrum.

The anhydrous nature of the inventive substance was characterized by its thermo gravimetric analysis, and the anhydrous nature of the compound was also confirmed by calculating the water content present in the compound by Karl Fischer (KF) method.

The report of thermo gravimetric analysis shows a total weight loss of 0.6% at a temperature range of 0-250$^{o}$C. The result indicates the anhydrous nature of the inventive substance obtained as per Example (1) of experimental section.

The present invention provides the thermogram of thermo gravimetric analysis of anhydrous form of Gatifloxacin substantially as depicted in Figure (1).

The present inventive substance is having a moisture content of 0.4% by KF method, which also confirms the anhydrous nature of the compound.

The X-ray powder diffraction pattern of anhydrous crystalline form was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source. The anhydrous crystalline form of Gatifloxacin has X-ray powder diffraction pattern essentially as shown in the Table-1. The X-ray powder diffraction pattern is expressed in terms of the 2 theta (degrees), and percentage of intensity (in %).

Table-1:

| 2 theta ($^{O}$) | Intensity (%) |
|---|---|
| 7.763 | 100 |
| 19.722 | 100 |
| 13.615 | 89.3 |
| 25.927 | 71.9 |
| 12.854 | 71.7 |
| 28.65 | 40.9 |
| 20.491 | 35.2 |
| 14.112 | 29.3 |
| 10.196 | 26.8 |
| 23.593 | 15.1 |
| 23.765 | 14.9 |
| 16.333 | 12.2 |
| 27.558 | 10.9 |
| 14.932 | 9.8 |
| 21.456 | 9.7 |
| 30.496 | 8.4 |
| 17.013 | 7.2 |
| 30.872 | 6.7 |
| 31.477 | 5.6 |
| 24.44 | 3.7 |

The present invention of anhydrous crystalline form of Gatifloxacin was characterized by its X-ray powder diffraction substantially as depicted in Figure (2).

The present invention provides the Differential Scanning Calorimetry thermogram of anhydrous crystalline form of Gatifloxacin. The Differential Scanning Calorimetry thermogram exhibits a significant endo peak at 188.35°C and substantially as depicted in Figure (3).

The present invention provides the Infrared data for anhydrous crystalline form of Gatifloxacin, which was measured by KBr-transmission method with significant peaks about 3327.7 and 1721.0 $cm^{-1}$.

The present invention provides the IR spectrum of anhydrous crystalline form of Gatifloxacin substantially as depicted in Figure (4).

Another embodiment of the present invention is to provide the preparation of novel anhydrous crystalline form of Gatifloxacin, which comprises;

i) refluxing azeotropically the hydrated form of Gatifloxacin in water-immiscible aromatic or aliphatic hydrocarbon solvents such as benzene, toluene, xylene, cyclohexane or ketone solvents such as methyl ethyl ketone, methyl isobutyl ketone, methyl tertiary butyl ketone, preferably toluene;

ii) cooling the reaction mixture of step (i) accompanied by stirring of the mixture till the solid mass crystallizes;

iii) isolating the solid obtained in step (ii);

iv) drying of the isolated compound of step (iii) at 30-70°C, preferably 50-60°C to afford anhydrous crystalline form of Gatifloxacin.

Thus, the present invention is directed to a novel anhydrous crystalline form of Gatifloxacin, which is non-hygroscopic, with residual solvents within permissible limits, which renders it well suited for pharmaceutical formulations.

The present invention will be explained in more detail with following examples but don't limit it in any way.

**REFERENCE EXAMPLE:**

**Preparation of hydrated form of Gatifloxacin:**

1-cyclo-6, 7-difluoro-1, 4-dihydro-4-oxo-8-methoxy quinolone-3-carboxylic acid (100 grams 0.339 moles) and 2-metyl piperazine (100 grams 1.0 mole) was added to Acetonitrile (500 ml) and the reaction mixture was slowly heated to the reflux temperature and stirred till the reaction was substantially complete. Then the solvent was distilled off completely and water (300 ml) was added to the residual mass and cooled the reaction mass to the temperature of 40-50$^{O}$C. The $P^{H}$ was adjusted towards acidic with Acetic acid (250 ml). The mass was filtered off and then $P^{H}$ of the filtrate was further adjusted to 6.0-8.0 with ammonia. The reaction mixture was cooled to a temperature of 10-15 $^{O}$C and stirred for 30-45 minutes. Thus, the obtained solid was successively recrystallized to afford Gatifloxacin; which had a moisture content ranging from 2.5 to 50.0%.

**EXAMPLE – 1:**

**Preparation of anhydrous crystalline form of Gatifloxacin:**

Gatifloxacin hydrate (obtained as per reference example) was suspended in toluene (250 ml) and heated to reflux to the temperature of 100-110$^{O}$C. Water was azeotropically removed, accompanied by cooling of the reaction mixture to 10-15$^{O}$C under stirring for 30-60 minutes

to crystallize the solid mass. The crystallized solid mass was filtered, washed with toluene (50 ml) and dried at 50-60°C to constant weight.

(Weight: 38 grams, 40%, M.C. by KF is 0.40% and Purity: 99.83%).

## DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig: 1 is characteristic thermogram of thermal gravimetric analysis of novel anhydrous crystalline form of Gatifloxacin, shows a total weight loss of 0.60% (w/w) at a temperature range of 0-250°C indicates the anhydrous nature of the inventive substance of crystalline form of Gatifloxacin.

Vertical axis: weight of the compound (in mg); Horizontal axis: Temperature (in °C).

Fig: 2 is characteristic X-ray powder diffraction pattern of the novel anhydrous crystalline form of Gatifloxacin.

Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees).

The significant 2 theta values (in degrees) obtained are 7.763, 10.196, 12.854, 13.615, 14.112, 14.932, 16.333, 17.013, 19.722, 20.491, 21.456, 23.593, 23.765, 24.44, 25.927, 27.558, 28.65, 30.496, 30.872, and 31.477.

Fig: 3 is characteristic Differential Scanning Calorimetric thermogram of novel anhydrous crystalline form of Gatifloxacin. The Differential Scanning Calorimetric thermogram exhibits a significant endo peak at 188.35°C.

Vertical axis: Temperature (in °C); Horizontal axis: Signal (in mV).

Fig: 4 is characteristic Infra Red spectrum of anhydrous crystalline form of Gatifloxacin with identified significant peaks at about 3327.7 and 1721.0 $cm^{-1}$.

Vertical axis: Wave length (in $Cm^{-1}$); Horizontal axis: Transmission (in %).

We claim:

1 .A novel anhydrous crystalline form of 1 – Cyclopropyl – 6 – fluoro – 8– methoxy- 7 – (3 – methyl –1–piperazinyl) – 4 – oxo – 1, 4 -dihydroquinoline –3 – carboxylic acid (Gatifloxacin).

2. The anhydrous crystalline form of Gatifloxacin of claim 1 has X-ray powder diffraction pattern with peaks at 7.763, 10.196, 12.854, 13.615, 14.112, 14.932, 16.333, 17.013, 19.722, 20.491, 21.456, 23.593, 23.765, 24.44, 25.927, 27.558, 28.65, 30.496, 30.872 and 31.477 degrees two theta.

3. The anhydrous crystalline form of Gatifloxacin of claim 2 having an X-ray powder diffraction pattern substantially as depicted in Figure (2).

4. The anhydrous crystalline form of Gatifloxacin of claim 1 having a differential scanning colorimetry thermogram which exhibits a characteristic endo peak at 188.35$^{o}$C.

5. The anhydrous crystalline form of Gatifloxacin of claim 4 having a differential scanning colorimetry thermogram substantially as depicted in Figure (3).

6. The anhydrous crystalline form of Gatifloxacin of claim 1 having an identified characteristic peaks at about 3327.7 and 1721.0 cm-$^{1}$ in the Infra red Spectrum.

7. The anhydrous crystalline form of Gatifloxacin of claim 6 having an Infra red Spectrum substantially as depicted in Figure (4).

8. A process for preparing the novel anhydrous crystalline form of 1 – Cyclopropyl – 6 – fluoro – 8– methoxy- 7 – (3 – methyl –1–piperazinyl) – 4 – oxo – 1, 4 - dihydroquinoline –3 – carboxylic acid (Gatifloxacin), which comprises;

i. refluxing azeotropically the hydrated form of Gatifloxacin in water-immiscible aromatic or aliphatic hydrocarbon solvents such as benzene, toluene, xylene, cyclohexane or ketone solvents such as methyl ethyl ketone, methyl isobutyl ketone, methyl tertiary butyl ketone, preferably toluene;

ii. cooling the reaction mixture of step (i) accompanied by stirring of the mixture till the solid mass crystallizes;

iii. isolating the solid obtained in step (ii);

iv. drying of the isolated compound of step (iii) at 30-70°C, preferably 50-60°C to afford anhydrous crystalline form of Gatifloxacin.

9. A process according to claim 8 of step (i) where in the aromatic hydrocarbon solvent is toluene.

10. The process for the preparation of novel anhydrous crystalline form of Gatifloxacin substantially as herein exemplified.

Dated this 04th day of April 2002

Signed)
Dr. Manne Satyanarayana Reddy,
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Dr. Reddy's Laboratories Limited.

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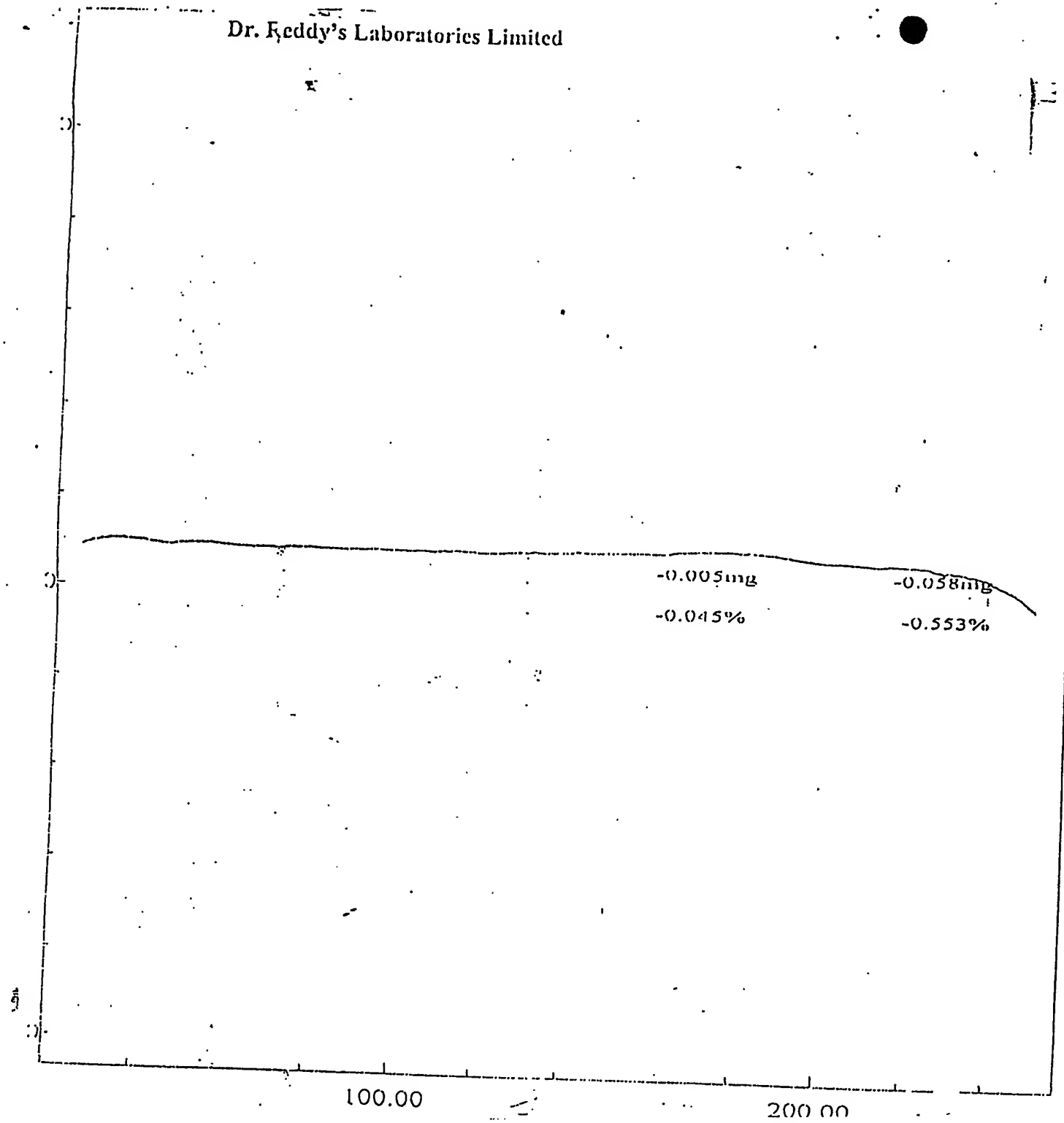

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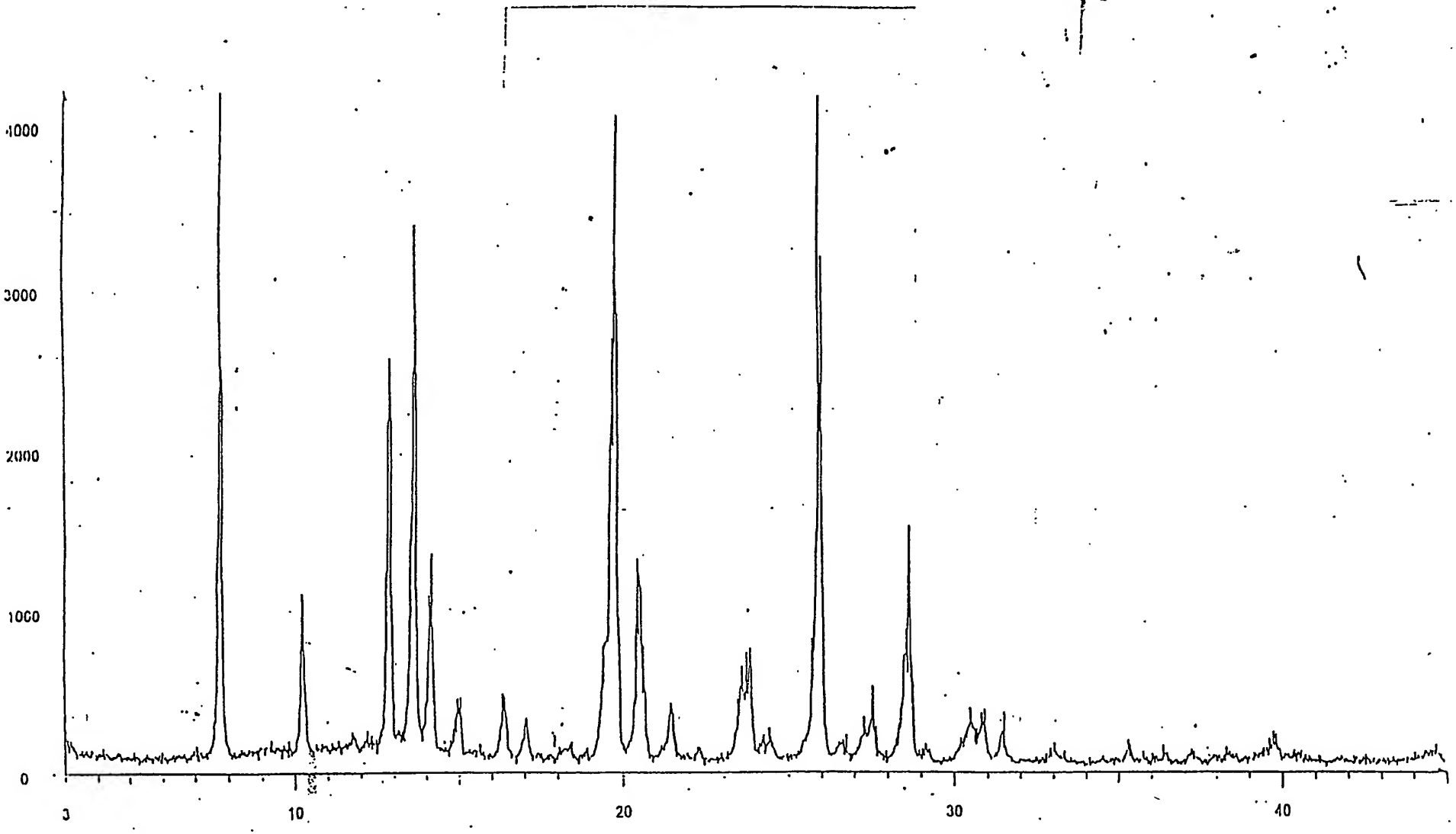


Fig 2

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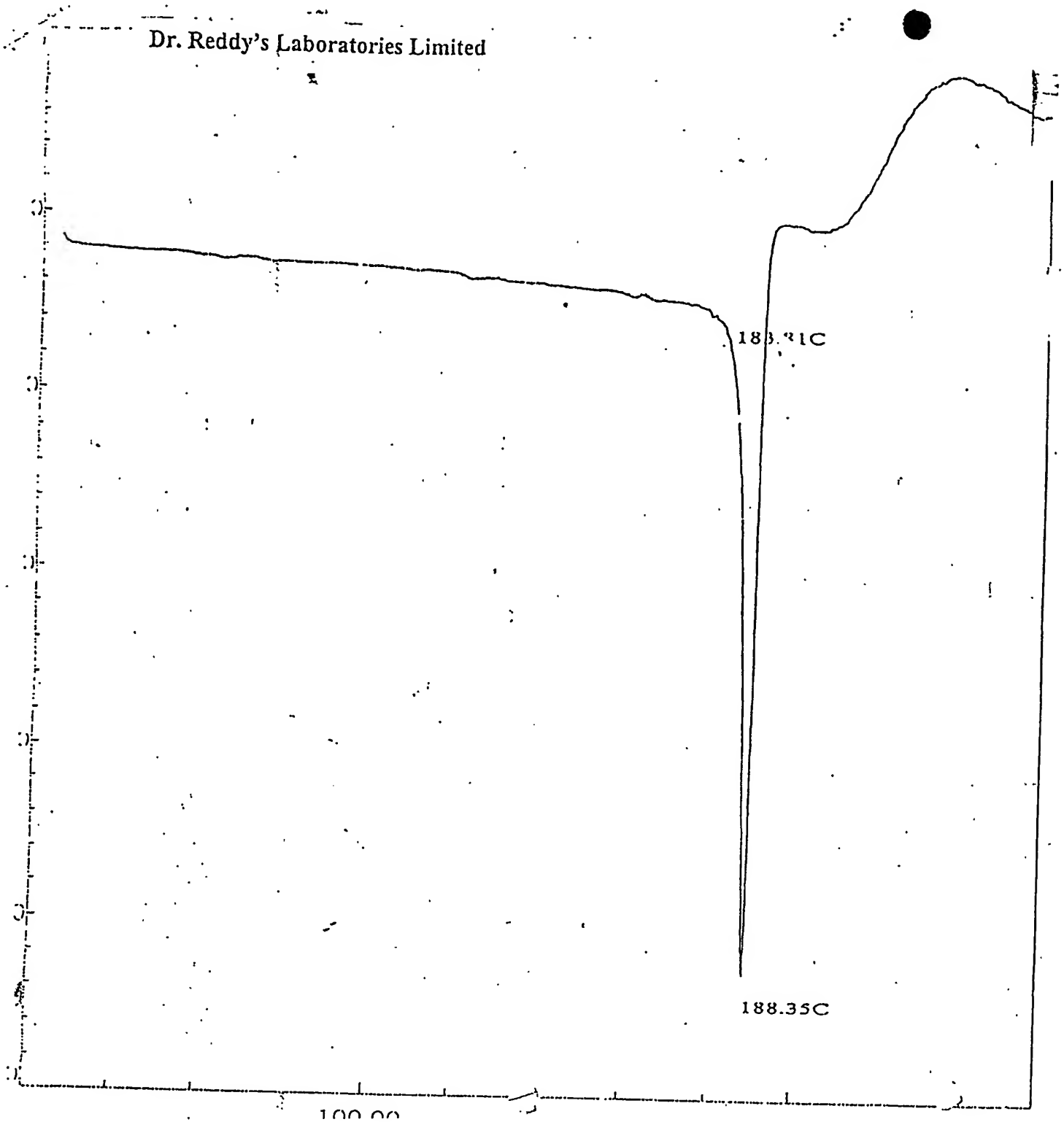

cm⁻¹
4000
3500
3000
2500
2000
1500
1000
500
0.81
1.26
3903.8
3759.8
3422.7
3327.7
2958.6
2513.3
2344.1
1461.2
1389.8
1276.3
1058.8
997.8
940.6
805.6
734.2
648.5
545.1

Fig 4